EPILEPSY CURRENTS

Current Review
In Epilepsy Genetics

Genetics of Epilepsy in Clinical Practice

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Genetics should now be part of everyday clinical epilepsy practice. Good data exist to provide empiric risks based on epilepsy syndrome diagnosis. Investigation of the molecular basis of some epilepsies is now a practical clinical task and is of clear value to the patient and family. In some cases, specific therapeutic decisions can now be made based on genetic findings, and this scenario of precision therapy is likely to increase in the coming years.

Tremendous strides have been made in unraveling the genetics of epilepsy in the last 2 decades. There have been many surprises such as discovery of the importance of de novo mutations, the complexities of phenotype–genotype relationships—one syndrome having multiple genetic causes (genetic heterogeneity) and one gene being associated with different phenotypes (pleiotropy)—the very large number of genes that appear to raise risk for epilepsy, and the emerging significance of somatic (postzygotic) mutations (1–3). Moreover, the dramatically reduced cost of genetic testing, the availability of gene panels, and even whole exome or whole genome sequencing at the clinical interface mean that genetics is rapidly becoming part of routine epilepsy practice, especially, but not exclusively, in pediatric settings.

This reality can appear daunting to the clinician without specific training in genetics. One is confronted with many choices in genetic testing; the results may appear as a veritable "alphabet soup" of gene names, and the interpretation of test results may not be straightforward. While we should turn to our clinical genetic colleagues for expert assistance, it behooves all practicing epileptologists to improve their "genetic literacy" to cope with this rapidly changing landscape, which impacts everyday clinical practice. Just as every epileptologist must have expertise in reading MRI scans, although not with the sophistication of a neuroradiologist, so should we aim to have basic competency in interpreting the implications and pitfalls of genetic data. Patients and families will certainly expect this! This review outlines clinical points in epilepsy genetics for the practicing neurologist, and the companion paper deals with genomic technologies, options for testing, and results interpretation (4).

How Do I Estimate Risk to Other Family Members?

It is axiomatic that precision in providing genetic risk information is dependent on precision in diagnosis. This requires both an accurate epilepsy diagnosis and a detailed family history. Tips on how to obtain optimal family history information are summarized elsewhere (1).

Epilepsies with Mendelian inheritance (e.g., autosomal dominant, autosomal recessive, X-linked) are rare, but the risk to relatives is high. Examples of dominant disorders are benign familial neonatal epilepsy (BFNE) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), where 50% of first-degree relatives will have the mutated gene, and of those, most will have clinical seizures (~85% of mutation carriers for BFNE [5] and ~70% for ADNFLE [6]). Recessive epilepsies are usually quite severe disorders (e.g., Lafora disease, Unverricht-Lundborg disease), and the risk to siblings is 25%; consideration of recessive disorders should be at the forefront when the parents may be consanguineous. X-linked disorders may not be obvious unless extensive pedigrees are constructed—X-linked recessive (boys only such as ARX-related epilepsies [7]); X-linked dominant (girls affected, boys severely affected or embryonic lethal such as double cortex syndrome and periventricular nodular heterotopia) (8); and the remarkable "girls-only" disorder (where carrier males are healthy) of PCDH-19–related epilepsy (9, 10). Each has quite different counseling implications.

In most epilepsies, however, inheritance is non-Mendelian, and risks to relatives are considerably lower. The precise genetic architecture of these disorders is still uncertain—that is, the number of genes involved (few or many) and their effect size—and this is a current research challenge (1, 11, 12). In many cases, there is no known family history in first- or even second-degree relatives, and the patient may appear surprised that the cause is genetic. The clinician must explain first that there may have been mild epilepsies in relatives that they were unaware of and further inquiry may be revealing, especially among the older relatives, and second, in complex inheritance, there may not necessarily be immediate relatives with the disorder, especially if the family size is small.

For the common epilepsies, empiric risks are well established. In genetic generalized epilepsies (GGE), the risk to first-degree relatives is increased approximately 8-fold com-

Epilepsy Currents, Vol. 15, No. 4 (July/August) 2015 pp. 192–196

pared with the general population, meaning that first-degree relatives have about an 8% chance of being affected by age 20; the risk to second-degree relatives is much less. In focal epilepsies, the risk to first-degree relatives is approximately 2.5-fold above the general population (11, 13).

There are uncommon exceptions to these general rules, where a penetrant mutant gene segregates in a Mendelian fashion causing common epilepsy phenotypes. Examples include mutations in *SLC2A1,* encoding the glucose transporter GLUT1, which are found in about 1% of GGE subjects (14). For focal epilepsies, mutations in genes *LGI1* and *DEPDC5* are currently the most commonly identified; these cause familial lateral temporal lobe epilepsy and familial focal epilepsy with variable foci (FFEVF), respectively. Clues to these disorders include obvious family history, the presence of auditory auras in *LGI1*-related families (15), and heterogeneous focal epilepsy phenotypes in *DEPDC5*-related epilepsies (16). The spectrum of epilepsies associated with *DEPDC5* mutation is rapidly expanding—small pedigrees may have exclusively nocturnal frontal lobe epilepsy or temporal lobe epilepsy thus not obviously suggesting FFEVF (16, 17). More remarkably, although MRIs are usually regarded as normal, some cases have subtle focal cortical dysplasia and occasionally more extensive focal malformations (18–20).

Why Should I Bother to Find a Genetic Cause?

Nihilistic views are sometimes expressed that finding a genetic cause does not alter management, and therefore genetic testing is unnecessary (21). If such views were ever defensible, they are certainly not now, for a number of reasons.

First, even if a condition is untreatable, patients and families nearly always want to know why the affliction has occurred. "Closure" of diagnosis is very important; it brings an end to the diagnostic odyssey, and families can stop searching for "answers" from multiple physicians or alternative medicine practitioners. This situation is particularly true when a previously healthy child develops an epileptic encephalopathy with refractory seizures and developmental regression. The parents may carry guilt, with a false belief that minor head knocks or vaccination (22) caused the disorder—identifying the true cause can provide considerable consolation and assuage unfounded blame. Even in milder familial epilepsies, subjects generally wish to know (23).

Second, a specific genetic diagnosis avoids unnecessary testing with repeated blood tests, MRIs, invasive biopsies, presurgical workup, and even intracranial electrodes in the vain hope that a focal lesion or some other cause might be found in an unsolved case of epileptic encephalopathy. In turn, this allows families to focus on the problem and not be distracted by searching for the cause. A genetic diagnosis may provide useful prognostic information regarding the natural history of the disorder as large case series accumulate—this has already happened with Dravet syndrome and PCDH19-related epilepsy and will occur in time for rarer epilepsies. Families often derive benefit by meeting similarly affected families, either in person or online. Family-driven groups focused on a specific disorder have become a powerful force for aggregation of accessible information, for effective public advocacy, and for encouraging and driving research. The empowerment derived by specific diagnosis, understanding the disorder and contributing to solve it cannot be underestimated (24–26).

Finally, a genetic diagnosis allows for specific counseling, as knowledge of the mutation then allows other interested family members to be tested, and much more precise information can be given, rather than broad empiric risk estimates discussed above. Where possible, this should be done in a genetic counseling environment with trained counselors and geneticists (27, 28). If there is a diagnosed familial epilepsy with a single major mutated gene, individual risk of family members can be easily determined by cascade testing, and risk to further children will also be apparent. De novo mutations provide a challenge; the risk to a further child is low, but not zero because of the possibility of parental mosaicism, which cannot easily be investigated. Counseling is also challenging when risk alleles (as opposed to genes determining Mendelian epilepsies) are detected (29); currently this is rarely a practical problem as few risk alleles are known, but this is likely to change in the near future.

The ethical, legal, and social concerns of genetic testing warrant systematic research (28,30). Concerns about the negative impact of a genetic diagnosis seem largely unfounded but need to be considered as testing becomes more widespread. Initial research supports the strong clinical impression that the impact of genetic information is largely positive; people want to know and find the data helpful (23, 31, 32).

Specific "Actionable" Genetic Findings

In addition to the general benefits of testing outlined above, there is a small but growing number of genetic diagnoses in which specific alterations in management are indicated. This may include the choice of conventional antiepileptic agents or the use of an alternative treatment.

Dravet syndrome, which is the result of mutations in *SCN1A* in 80% of cases, is generally easy to diagnose after a few years of life when the characteristic evolution of seizure types and developmental stagnation has occurred. There is some evidence that early aggressive therapy improves outcome, so testing should be considered early (32–34). Specific guidelines for testing are available—Dravet syndrome should be considered in infants with febrile seizures presenting around 6 months of age, especially those with prolonged and recurrent febrile seizures, hemiclonic seizures, and seizures induced by bathing (35). Recognition in adult life may lead to better seizure control and cognitive outcome (36). Sodium channel blockers such as lamotrigine and carbamazepine should be avoided, whereas valproic acid, topiramate, clobazam, and stiripentol appear to be beneficial (33, 34). Unfortunately, at present, these guidelines are based on case series evidence, with the exception of the use of stiripentol where controlled trials have shown benefit (37).

The epileptic encephalopathies associated with mutations in *SCN2A* and *SCN8A* are gradually becoming better defined (38, 39) and appear to be rarer than Dravet syndrome. Their profile of drug responsiveness may be different as the proteins encoded are localized to excitatory neurons, whereas the *SCN1A* protein appears to be mainly on inhibitory interneurons. Indeed, for *SCN8A* encephalopathy, sodium channel blockers may be effective in some cases (39).

Highlight Points

- Genetic literacy is essential for the practicing epileptologist.
- Good data are available on empiric familial risks.
- Molecular diagnosis is valuable for the patient and family.
- Genetic findings influence management.
- Specific precision therapies are emerging.

Loss of function mutations in the potassium channel gene *KCNQ2* have been robustly associated with both BFNE and a severe epileptic encephalopathy resulting from de novo mutations. The novel drug ezogabine (retigabine) specifically targets these channels, but unfortunately toxicity to the retina, skin, and nails may limit its use, and there are little data on its effectiveness in *KCNQ2* encephalopathy. However, recent experience suggests that sodium channel blockers, carbamazepine and phenytoin, are effective in this disorder (40).

Mutations in *SLC2A1*, encoding the glucose transporter GLUT1, have long been known to cause a severe infantile encephalopathy with low CSF glucose that responds partially to the ketogenic diet. The spectrum of epilepsies associated with GLUT1 deficiency now includes a small proportion of GGE, especially early-onset absence epilepsy and, less commonly, other absence epilepsies as well as about 5% of patients with epilepsy with myoclonic-atonic seizures (41, 42). Some patients may have paroxysmal exercise-induced dyskinesia, increased seizures before meals, mild intellectual impairment, or cerebellar signs, which are clinical clues to the diagnosis. Many patients with mild GLUT1 deficiency respond to conventional antiepileptic drugs, but awareness of the diagnosis emphasizes the option of ketogenic diet therapy for refractory cases.

Pyridoxine-dependent epilepsy is a well-known, albeit rare, infantile epilepsy, generally diagnosed by clinical suspicion and response to pyridoxine. Mutation detection in *ALDH7A1* can provide confirmation and be used to rapidly screen at-risk siblings (43). The related disorder, pyridoxamine 5′-phosphate oxidase deficiency, owing to mutations in *PNPO*, may only respond to pyridoxal 5′-phosphate, but the relationship of mutations to treatment response remains unclear (44).

There is now a great deal of interest in novel precision therapies based on molecular findings. Quinidine reverses the in vitro gain of function seen with *KCNT1* mutations in epilepsy with migrating focal seizures of infancy, and a clinical response to quinidine has been observed (45, 46). Similarly, in a patient with a mutation in *GRIN2A*, encoding a glutamate receptor subunit, memantine therapy appeared effective (47). The recent discovery of the importance of mutations in *DEPDC5* (16–20), which is now known to be a regulator of mTOR, raises the possibility of treatment with rapamycin analogues. All of these observations will need careful double-blind trials to establish efficacy.

Conclusion

Genetics is transforming clinical practice in epilepsy, especially in children. Useful clinical information can be provided to families, and a specific molecular diagnosis, where possible, adds greatly to the accuracy of the information. The promise of precision therapies is becoming a reality and may eventually become widely applicable.

References

1. Thomas RH, Berkovic SF. The hidden genetics of epilepsy—A clinically important new paradigm. *Nat Rev Neurol* 2014;10:283–292.
2. Poduri A, Evrony GD, Cai X, Walsh CA. Somatic mutation, genomic variation, and neurological disease. *Science* 2013;341:1237758. doi:10.1126/science1237758.
3. Noebels J. Pathway-driven discovery of epilepsy genes. *Nat Neurosci* 2015;18:344–350.
4. Mefford HC. Clinical genetic testing in epilepsy. *Epilepsy Curr* 2015;15:206–210.
5. Plouin P, Neubauer BA. Benign familial and non-familial neonatal seizures. In: *Epileptic Syndromes in Infancy, Childhood and Adolescence*. (Bureau M, Genton P, Dravet C, Delgado-Escueta A, Tassinari CA, Thomas P, Wolf P, eds.) Montrouge, France: John Libbey Eurotext, 2012:77–88.
6. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, Andermann F, Desbiens R, Keene D, Cendes F, Manson JI, Constantinou JEC, McIntosh A, Berkovic SF. Autosomal dominant nocturnal frontal lobe epilepsy: A distinctive clinical disorder. *Brain* 1995;118:61–73.
7. Shoubridge C, Fullston T, Gécz J. ARX spectrum disorders: Making inroads into the molecular pathology. *Hum Mutat* 2010;31:889–900.
8. Guerrini R, Dobyns WB. Malformations of cortical development: Clinical features and genetic causes. *Lancet Neurol* 2014;13:710–726.
9. Hynes K, Tarpey P, Dibbens LM, Bayly MA, Berkovic SF, Smith R, Al Raisi Z, Turner SJ, Brown NJ, Desai TD, Haan E, Turner G, Christodoulou J, Leonard H, Gill D, Stratton MR, Gecz J, Scheffer IE. Epilepsy and mental retardation limited to females with PCDH19 mutations can present de novo or in single generation families. *J Med Genet* 2010;47:211–216.
10. Depienne C, LeGuern E. PCDH19-related infantile epileptic encephalopathy: An unusual X-linked inheritance disorder. *Hum Mutat* 2012;33:627–634.
11. Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: Unravelling the genetics of the epilepsies. *Lancet Neurol* 2008;7:231–245.
12. Epi4K Consortium. Epi4K: Gene discovery in 4,000 genomes. *Epilepsia* 2012;53:1457–1467.
13. Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, Buchhalter JR, Ottman R. Familial risk of epilepsy: A population-based study. *Brain* 2014;137:795–805.
14. Arsov T, Mullen SA, Rogers S, Phillips AM, Lawrence KM, Damiano JA, Goldberg-Stern H, Afawi Z, Kivity S, Trager C, Petrou S, Berkovic SF, Scheffer IE. GLUT1-deficiency in the idiopathic generalised epilepsies. *Ann Neurol* 2012;72:807–815.
15. Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley TA, Hauser WA. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. *Neurology* 2004;62:1120–1126.
16. Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, Crompton DE, Hughes JN, Bellows ST, Klein KM, Callenbach PM, Corbett MA, Gardner AE, Kivity S, Iona X, Regan BM, Weller CM, Crimmins D, O'Brien TJ, Guerrero-López R, Mulley JC, Dubeau F,

Licchetta L, Bisulli F, Cossette P, Thomas PQ, Gecz J, Serratosa J, Brouwer OF, Andermann F, Andermann E, van den Maagdenberg AM, Pandolfo M, Berkovic SF, Scheffer IE. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. *Nat Genet* 2013;45:546–551.
17. Picard F, Makrythanasis P, Navarro V, Ishida S, de Bellescize J, Ville D, Weckhuysen S, Fosselle E, Suls A, De Jonghe P, Vasselon Raina M, Lesca G, Depienne C, An-Gourfinkel I, Vlaicu M, Baulac M, Mundwiller E, Couarch P, Combi R, Ferini-Strambi L, Gambardella A, Antonarakis SE, Leguern E, Steinlein O, Baulac S. DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 2014;82:2101–2106.
18. Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, Hodgson BL, Licchetta L, Provini F, Bisulli F, Vadlamudi L, Gecz J, Connelly A, Tinuper P, Ricos MG, Berkovic SF, Dibbens LM. Mutations in mTOR regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol* 2014;75:782–787.
19. Baulac S, Ishida S, Marsan E, Miquel C, Biraben A, Nguyen DK, Nordli D, Cossette P, Nguyen S, Lambrecq V, Vlaicu M, Daniau M, Bielle F, Andermann E, Andermann F, Leguern E, Chassoux F, Picard F. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. *Ann Neurol* 2015;77:675–683.
20. D'Gama AM, Geng Y, Couto JA, Martin B, Boyle EA, LaCoursiere CM, Hossain A, Hatem NE, Barry BJ, Kwiatkowski DJ, Vinters HV, Barkovich AJ, Shendure J, Mathern GW, Walsh CA, Poduri A. Mammalian target of rapamycin pathway mutations cause hemimegalencephaly and focal cortical dysplasia. *Ann Neurol* 2015;77:720–725.
21. Delgado-Escueta AV, Bourgeois BF. Debate: Does genetic information in humans help us treat patients? PRO—genetic information in humans helps us treat patients. CON—genetic information does not help at all. *Epilepsia* 2008;49(suppl 9):13–24.
22. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: A retrospective study. *Lancet Neurol* 2006;5:488–492.
23. Vears DF, Dunn KL, Wake SA, Scheffer IE. "It's good to know": Experiences of gene identification and result disclosure in familial epilepsies. *Epilepsy Res* 2015;112:64–71.
24. Walters J, Wells-Kilpatrick K, Pandeleos T. My epilepsy story—PCDH19 alliance. *Epilepsia* 2014;55:968–969.
25. Nakagawa JA. My epilepsy story—The Tuberous Sclerosis Alliance. *Epilepsia* 2014;55:494–495.
26. Maxwell A. My epilepsy story—Muir Maxwell Trust. *Epilepsia* 2014;55:1690–1692.
27. Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE. Genetic testing in the epilepsies—Report of the ILAE Genetics Commission. *Epilepsia* 2010;51:655–670.
28. Poduri A, Sheidley BR, Shostak S, Ottman R. Genetic testing in the epilepsies—Developments and dilemmas. *Nat Rev Neurol* 2014;10:293–299.
29. De Wolf V, Brison N, Devriendt K, Peeters H. Genetic counseling for susceptibility loci and neurodevelopmental disorders: The del15q11.2 as an example. *Am J Med Genet A* 2013;161A:2846–2854.
30. Shostak S, Ottman R. Ethical, legal, and social dimensions of epilepsy genetics. *Epilepsia* 2006;47:1595–1602.
31. Okeke JO, Tangel VE, Sorge ST, Hesdorffer DC, Winawer MR, Goldsmith J, Phelan JC, Chung WK, Shostak S, Ottman R. Genetic testing preferences in families containing multiple individuals with epilepsy. *Epilepsia* 2014;55:1705–1713.
32. Brunklaus A, Dorris L, Ellis R, Reavey E, Lee E, Forbes G, Appleton R, Cross JH, Ferrie C, Hughes I, Jollands A, King MD, Livingston J, Lynch B, Philip S, Scheffer IE, Williams R, Zuberi SM. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. *Dev Med Child Neurol* 2013;55:154–161.
33. Chiron C, Dulac O. The pharmacologic treatment of Dravet syndrome. *Epilepsia* 2011;52(suppl 2):72–75.
34. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain* 2012;135:2329–2336.
35. Hirose S, Scheffer IE, Marini C, De Jonghe P, Andermann E, Goldman AM, Kauffman M, Tan NC, Lowenstein DH, Sisodiya SM, Ottman R, Berkovic SF; Genetics Commission of the International League Against Epilepsy. SCN1A testing for epilepsy: Application in clinical practice. *Epilepsia* 2013;54:946–952.
36. Catarino CB, Liu JY, Liagkouras I, Gibbons VS, Labrum RW, Ellis R, Woodward C, Davis MB, Smith SJ, Cross JH, Appleton RE, Yendle SC, McMahon JM, Bellows ST, Jacques TS, Zuberi SM, Koepp MJ, Martinian L, Scheffer IE, Thom M, Sisodiya SM. Dravet syndrome as epileptic encephalopathy: Evidence from long-term course and neuropathology. *Brain* 2011;134:2982–3010.
37. Kassaï B, Chiron C, Augier S, Cucherat M, Rey E, Gueyffier F, Guerrini R, Vincent J, Dulac O, Pons G. Severe myoclonic epilepsy in infancy: A systematic review and a meta-analysis of individual patient data. *Epilepsia* 2008;49:343–348.
38. Nakamura K, Kato M, Osaka H, Yamashita S, Nakagawa E, Haginoya K, Tohyama J, Okuda M, Wada T, Shimakawa S, Imai K, Takeshita S, Ishiwata H, Lev D, Lerman-Sagie T, Cervantes-Barragán DE, Villarroel CE, Ohfu M, Writzl K, Gnidovec Strazisar B, Hirabayashi S, Chitayat D, Myles Reid D, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Hayasaka K, Matsumoto N, Saitsu H. Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome. *Neurology* 2013;81:992–998.
39. Larsen J, Carvill GL, Gardella E, Kluger G, Schmiedel G, Barisic N, Depienne C, Brilstra E, Mang Y, Nielsen JE, Kirkpatrick M, Goudie D, Goldman R, Jähn JA, Jepsen B, Gill D, Döcker M, Biskup S, McMahon JM, Koeleman B, Harris M, Braun K, de Kovel CG, Marini C, Specchio N, Djémié T, Weckhuysen S, Tommerup N, Troncoso M, Troncoso L, Bevot A, Wolff M, Hjalgrim H, Guerrini R, Scheffer IE, Mefford HC, Møller RS; EuroEPINOMICS RES Consortium CRP. The phenotypic spectrum of SCN8A encephalopathy. *Neurology* 2015;84:480–489.
40. Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, Podesta B, Thibert RL, Shapiro KA, Guerrini R, Scheffer IE, Marini C, Cilio MR. Early and effective treatment of KCNQ2 encephalopathy. *Epilepsia* 2015;56:685–691. doi:10.1111/epi.
41. Scheffer IE. GLUT1 deficiency: A glut of epilepsy phenotypes. *Neurology* 2012;78:524–525.
42. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). *Curr Neurol Neurosci Rep* 2013;13:342. doi:10.1007/s11910-013-0342-7.
43. Stockler S, Plecko B, Gospe SM Jr, Coulter-Mackie M, Connolly M, van Karnebeek C, Mercimek-Mahmutoglu S, Hartmann H, Scharer G, Struijs E, Tein I, Jakobs C, Clayton P, Van Hove JL. Pyridoxine dependent epilepsy and antiquitin deficiency: Clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. *Mol Genet Metab* 2011;104:48–60.
44. Mills PB, Camuzeaux SS, Footitt EJ, Mills KA, Gissen P, Fisher L, Das KB, Varadkar SM, Zuberi S, McWilliam R, Stödberg T, Plecko B, Baumgartner MR, Maier O, Calvert S, Riney K, Wolf NI, Livingston JH, Bala P, Morel CF, Feillet F, Raimondi F, Del Giudice E, Chong WK, Pitt M, Clayton PT. Epilepsy due to PNPO mutations: Genotype, environment and treatment affect presentation and outcome. *Brain* 2014;137:1350–1360.

45. Milligan CJ, Li M, Gazina EV, Heron SE, Nair U, Trager C, Reid CA, Venkat A, Younkin DP, Dlugos DJ, Petrovski S, Goldstein DB, Dibbens LM, Scheffer IE, Berkovic SF, Petrou S. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann Neurol* 2014;75:581–590.
46. Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol* 2014;76:457–461.
47. Pierson TM, Yuan H, Marsh ED, Fuentes-Fajardo K, Adams DR, Markello T, Golas G, Simeonov DR, Holloman C, Tankovic A, Karamchandani MM, Schreiber JM, Mullikin JC; PhD for the NISC Comparative Sequencing Program, Tifft CJ, Toro C, Boerkoel CF, Traynelis SF, Gahl WA. *GRIN2A* mutation and early-onset epileptic encephalopathy: Personalized therapy with memantine. *Ann Clin Transl Neurol* 2014;1:190–198.